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10/694,520	10/27/2003	Gail Bishop	17023-019001 / 02049	2261
53137	7590	04/19/2006	EXAMINER	
VIKSNINS HARRIS & PADYS PLLP P.O. BOX 111098 ST. PAUL, MN 55111-1098			MCGILLEM, LAURA L	
			ART UNIT	PAPER NUMBER
			1636	
DATE MAILED: 04/19/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

10/694,520

Applicant(s)

BISHOP ET AL.

Examiner

Laura McGillem

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 2/9/2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-31 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 6-31 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 2/9/06.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

It is noted that Applicants have amended claims 1, 13-14, 20 and 30-31 and cancelled claim 5 in the response filed 02/09/2006. Claims 1-4 and 6-31 are under examination.

#### ***Information Disclosure Statement***

The receipt of an information disclosure statement (IDS) submitted on 02/09/2006 is noted. Accordingly, the information disclosure statement is being considered by the examiner.

#### ***Claim Rejections - 35 USC § 112***

Claims 1-4 and 6-31 are rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

This rejection is being maintained for reasons of record stated in the previous Office Action, mailed 8/10/2005 and for the reasons outlined below.

Applicants submit that a showing of possession of the claimed invention is a determination reached by considering a number of factors including level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics or disclosed correlation between structure and function and the method of making the invention. Applicants submit that disclosure of any combination of said

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identifying characteristics that distinguish the claimed invention would lead the skilled artisan to conclude that Applicant was in possession of the claimed invention.

Applicants also submit that the question of written description should not be raised for original claims in a mature technology even if only the method of making the invention and function of the invention are disclosed. Applicants cite case law from *In re* Hayes Microcomputer Products, which states that "(A)n inventor is not required to describe every detail of his invention". Applicant further asserts that the specification supplies adequate written description for the claimed invention, positive negative selection vectors were known at the time of the application filing and the skilled artisan would know how to make the claimed construct once the inventors instructed the skilled artisan what pieces needed to go in the construct.

Applicants further submit that the citation of the Wang et al and Norgen review articles by the Examiner appear to be an enablement rejection rather than a written description rejection. Applicants submit that the presence of a potentially inoperative embodiment within the scope of a claim does not necessarily render a claim non-enabled.

Applicants' arguments have been considered but are not persuasive because the claimed vector and method of disrupting genes of interest are so broad as to encompass a somatic cell gene targeting vector for any gene of interest and a method of use of that vector to target any gene of interest.

Although Applicants submit that support for written description of the claimed invention lies in factors including level of skill and knowledge in the art, partial structure,

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physical and/or chemical properties, functional characteristics or disclosed correlation between structure and function and the method of making the invention, the instant specification has not provided sufficient disclosure of these factors to show that Applicants have possession of the claimed genus of vectors specific for targeting any of an enormous number of genes of interest. Although an inventor is not required to describe every detail of an invention in a mature technology, there must be sufficient description of the structure of a representative species of a genus to relate the species structure to its function and suggest that the other members would have the same or similar function, claimed as a method for disrupting a gene of interest in a somatic cell. In order for the skilled artisan to construct the claimed gene targeting vector, the skilled artisan would need to know the sequence of two genomic segments of a gene of interest and their locations in order to construct a targeting vector that would disrupt the gene of interest. For example, in order to disrupt known Gene X, the sequence of Gene X, including locations of exons and introns would be required. In addition, unless the entire sequence of Gene X is to be disrupted, the skilled artisan would need to know the sequences associated with important functional domains in the gene of interest. These targeted sites on Gene X must be in appropriate location to be able to use site-specific recombination to disrupt the gene. Although the abilities necessary to construct this vector are available to the skilled artisan, neither the skilled artisan or the inventors have possession of the genomic structure of an enormous number of genes of interest in a gene targeting vectors with the function of gene disruption without further trial and error experimentation in order to "instruct the person of skill what pieces need to go into

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the construct". Although the Applicants have provided a construct to disrupt Traf, the gene encoding Traf does not represent the genus of any other unrelated genes of interest.

Citation of the Wang et al (i.e. not all gene targeting results in functional disruption) and Norgen (i.e. genes without active promoters can not be targeted with a promoterless vector) review articles was not intended as support for an enablement rejection. Instead Wang et al and Norgen were cited in order to illustrate art-recognized issues regarding targeting of genes for disruption regarding the length of the targeted gene, chromosomal location and proximity to a promoter, all of which relate to the appropriate structure of a particular targeting vector. Although Wang et al do teach difficulties with inducing homologous recombination in mouse ES cells, Wang et al also teach that gene targeting in somatic cells is "more difficult" than in mouse ES cells (see page 3 of 8, right column, 2<sup>nd</sup> paragraph). The teachings of Wang et al and Norgen are meant to emphasize that the specification does not provide sufficient descriptive support for the complete genus of claimed gene targeting vector for the claimed function of disrupting any gene of interest, since the claimed function is complex.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 6-7 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi et al (U.S. Patent No. 5,631,153, of record), in view of Sedivy et al. (of record).

The rejections of claims 1-7 and 11-12 are being maintained for reasons of record in the previous Office action (mailed 8/10/2005) and for reasons that are outlined below.

Applicants submit that Capecchi et al do not disclose polyadenylation sequences operably linked to the positive selection marker and do not disclose excision of the positive selection sequences using site-specific recombination sequences, such as loxP sequences. Applicants submit that Capecchi et al teach that the positive selection sequences can be excised by homologous recombination and a detailed method where the positive selection marker is not promoterless.

Applicants further submit that Sedivy does not remedy the deficiencies of Capecchi et al because Sedivy does not teach a promoterless PNS vector, and therefore cannot teach the use of a polyadenylation sequence with a promoterless PNS vector. Applicants submit that Sedivy provides no technical details of sequential targeting of second allele. Applicants submit that Sedivy references a paper in which a Cre/lox system is used to remove a PNS cassette (positive-negative selection cassette that includes both a promoter-driven neo resistance gene as well as a thymidine kinase gene) from a targeting vector. Applicants submit that Sedivy does not teach or suggest a promoterless positive selection marker and therefore cannot teach the combination of a promoterless positive selection marker in combination with a Cre/lox system.

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Applicants submit that neither reference discusses the use of a weak promoter and does not specifically mention the PGK or RSV promoter.

Applicant's arguments filed 2/9/2006 have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants submit that they teach a detailed method where the positive selection marker is not promoterless, however Capecchi et al do teach some embodiments in which the vector is promoterless (see column 6, lines 42, description of Fig 9, column 9, lines 10-14 and column 26, example 6, in particular). Although Capecchi et al do not disclose polyadenylation sequences operably linked to the positive selection marker and do not disclose excision of the positive selection sequences using site-specific recombination sequences, Sedivy et al does teach targeted homologous gene recombination in somatic cells using positive negative selection (PNS) vectors and using promoterless vectors (see page 88, left column, paragraph 2, bridging to right column, and Figure 1, in particular). Although Applicants submit that Sedivy does not teach or suggest a promoterless positive selection marker, Sedivy et al do teach the use of a polyadenylation sequence with the PNS and promoterless vectors and also teach that the Cre-Lox system of recombination can be used for specific recombination (see



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Figure 1 and 2, and page 90, left column, paragraph 2). Therefore, it is the combination of the teaching of Capecchi et al and Sedivy et al that renders the claimed invention obvious.

Applicant's arguments, see page 12, filed 2/9/2006, with respect to the vector comprising a weak promoter or a PGK or RSV promoter have been fully considered and are persuasive. The rejections of claims 8-10 have been withdrawn.

### ***Conclusion***

No claims are allowed. Previous rejections that have not been addressed herein are hereby withdrawn.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Laura McGillem, PhD  
4/14/2006

  
DAVID GUZO  
PRIMARY EXAMINER